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Evaluation of the Effect of Serum Therapy on the Serum Level of Bilirubin in Term Neonates Hospitalized Due to Non-Hemolytic Hyperbilirubinemia and Treated with Phototherapy

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Abstract

Background and objective: neonatal hyperbilirubinemia is one of the most common causes of hospitalization and it is one of the health problems around the world. As various centers adopt different methods in management of neonatal hyperbilirubinemia and the conditions for prescribing fluids and given the controversial results of studies conducted in this regard and as intravenous fluids in combination with phototherapy have been used routinely since several years ago for treatment of non-conjunctional non-hemolytic hyperbilirubinemia without special study in the neonatal unit of Shahid Motahari Hospital of Urmia, this research was conducted to evaluate the effect of prescription of intravenous fluids on non-hemolytic neonatal jaundice during phototherapy in the neonatal unit of Shahid Motahari Hospital in Urmia.Materials and Methods: In this clinical trial study, 120 neonates hospitalized due to jaundice were randomly assigned to control and intervention groups. In these two groups, the neonates were homogenized in terms of number, gender, age at hospitalization time, birth weight and weight at hospitalization time. The data were analyzed by using SPSS Version 21. Results: The mean of drop in bilirubin level at 6, 12 and 24 hours after phototherapy was not significantly different in the intervention group (received serum) and control group (did not receive serum). Additionally, the duration of phototherapy to achieve dischargeable bilirubin level (bilirubin under 13) was 38.8 hours in the intervention group and 41.31 hours in the control group, which was not significantly different.Conclusion: results of our study showed that there was no statistically significant difference between patients of intervention and control groups in terms of rate of reduction in bilirubin and the time required for phototherapy to discharge. According to the statistics, there was no significant difference between the two groups in rate and level of reduction in bilirubin at 6, 12, and 24 hours and the time required for phototherapy and the complications during phototherapy.

Keywords: Hyperbilirubinemia, Non-Conjugated Hyperbilirubinemia, Term Neonates, Serum Therapy

Introduction

Jaundice is very common in neonates and is often associated with relatively high hemoglobin, immature liver conjugation, and bilirubin reabsorption into bloodstream through the enterohepatic pathway (Rennie et al., 2017). According to new Jaundice Control Guidelines, severe jaundice, which requires blood exchange, refers to serum bilirubin more than 25 mg / dl, while bilirubin was considered to be more than 20 mg / dl since July 2007-2012 (Bhutani et al., 2016). Hyperbilirubinemia of neonates can cause brain damage, including transient bilirubin encephalopathy and kernicterus, and even death of neonate (Zhang, 2018; Al-Lawama et al., 2018).

Selecting a suitable and harmless treatment method is crucial to prevent the major complications. Various methods are used for treatment of jaundice, such as phototherapy, blood exchange, and drug therapies such as phenobarbital, metalloporphyrin, and non-absorbable substances bond to bilirubin, such as activated charcoal and agar (Martin et al., 2007). Phototherapy has been used as a safe and effective method for the treatment of neonatal hyperbilirubinemia in recent years. Although phototherapy has some undesirable effects, such as diarrhea, dehydration and oxidative stress, no other method has been developed for the treatment of hyperbilirubinemia so far to have complications less than phototherapy and can be used easily (Maisels & McDonagh, 2008; Kanmaz et al., 2017). In addition to the adverse effects mentioned above, it has been shown that phototherapy may also have adverse effects on chromosomes in some animal

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and clinical studies (Aycicek et al., 2008).

Current estimates show that about 6% of neonates are treated in over 35-week pregnancy with phototherapy (Chang et al., 2016). In this method, visible light with a particular wavelength, especially blue light, is used to convert non-conjugated bilirubin non-soluble in water to some types of bilirubin solved in water without need for liver conjugation and excreted from body (Martin et al., 2007). If phototherapy is discontinued early, non-conjugated bilirubin is reproduced and re-phototherapy would be required. Most of the previous studies have reported recurring hyperbilirubinemia over a short period of 24 hours (Chang et al., 2017). If severe jaundice is observed in breastfed neonates, the Pediatrics Academy and Neonatal Jaundice Subcommittee recommendation would be breastfeeding along with baby formula in order to increase caloric intake and reduce intestinal and liver circulation (Iranpoor et al., 2004).

As various centers adopt different methods in management of neonatal hyperbilirubinemia and the conditions for prescribing fluids and given the controversial results of studies conducted in this regard and as intravenous fluids in combination with phototherapy have been used routinely since several years ago for treatment of non-conjunctional non-hemolytic hyperbilirubinemia without special study in the neonatal unit of Shahid Motahari Hospital of Urmia, and given the fact that serum therapy has its own complications, such as the risk of local and systemic infection, painfulness, increased therapeutic costs, and the inability to continue phototherapy at home, this research was conducted to evaluate the effect of prescription of intravenous fluids on non-hemolytic neonatal jaundice during phototherapy in the neonatal units of Shahid Motahari Hospital in Urmia.

Methods and Materials

This clinical trial research was conducted in the neonatal unit of Shahid Motahari Hospital in Urmia during 2008-20098. A total of 120 neonates (60 neonates in the intervention group and 60 neonates in the control group) were randomly selected. The included neonates were healthy full-term neonates with serum bilirubin level higher than 18 and less than 25 mg / dl, who had had icterus from the second day of life afterwards and for less than 14 days. A random selection was used to select the control and intervention groups, in such a way that one neonate who had jaundice and meet the primary inclusion criteria of study criteria was included into intervention group as a neonate NO 1 and the second neonate admitted at the same day and met the inclusion criteria of study was included into control group as neonate NO 2 and rest of neonates were selected and assigned into these two groups based on the same procedure.

In the control group, phototherapy began with eight-lamp phototherapy and feeding continued by breastfeeding or baby formula. In the intervention group, in addition to eight-lamp phototherapy and continued breastfeeding or baby formula, intravenous fluid therapy with 5% dextrose (80 cc / kg of body weight on the second day of birth and 120 cc / kg of body weight since third day afterwards) along with electrolyte was given for neonate, and the serum therapy was discontinued in both groups when the bilirubin level reached 15 mg / dl or less and phototherapy was discontinued when bilirubin level reached 13 mg / dl.

To control the level of bilirubin in the neonate, bilirubin was measured every 6 hours in the first 24 hours after beginning of treatment, and then, based on the initial level of bilirubin. The bilirubin level was controlled every 6 hours for bilirubin more than 20 mg / dl. One reason to select the 6-hour interval to control the bilirubin at the beginning of phototherapy was to ensure the proper effect of phototherapy at the beginning of treatment on reducing the level of bilirubin and using the therapy needed for patients who did not give a favourable response to phototherapy and needed to select other therapies such as blood exchange. This measurement was performed using intravenous serum sample. After drop in level of bilirubin, it was performed based on the level of drop in bilirubin at required intervals (bilirubin control every 12 or 24 hours). To control the possible complications in the control and intervention groups, complications checklist was used.

Complications of phototherapy were common in both groups and the complications of serum therapy were also listed. In phototherapy complications, the checklist included dehydration, lethargy or restlessness, stool looseness, eye injury, tanned child syndrome, and possible risks including electric shock and burns. Serum therapy complications included infection of the catheter site and sepsis and serum leakage into the skin and skin necrosis. In order to control these cases, a Pediatric resident examined the subjects daily, including a general examination during the hospitalization days and at the discharge time, daily weight, level of daily nutrition, and complaints created over the past 24 hours. They were stated and recorded. In this research, placebo was not used for control group. The obtained data were analyzed by SPSS 21 software. Descriptive statistics were used for descriptive analysis and Chi-square and TEST-T tests were used to analyze and compare the means of the two groups.

Results

In this research, 120 neonates hospitalized due to jaundice were examined. These neonates were randomly assigned to the control and intervention groups. In these two groups, the neonates were homogenized in terms of number, gender, age at hospitalization time, birth weight and weight during hospitalization. Out of 60 neonates included in the intervention group, 22 were male (36.6%) and 38 were

females (63.4%), and 29 controls (4.48%), and in the control group, 29 were male (48.8%) and 31 (51.6%) were female. Mean age was between 3 and 11 days in the intervention group and between 3 and10 days in the control group. The mean age at hospitalization time was 4.9 days in the intervention group and 5.5 days in control group. The mean weight at the hospitalization time was 3.80 kg in intervention group and 3.40 kg in control group. The mean of hemoglobin level was 7.15 in the intervention group and 4.15 in the control group. The mean level of reticulocyte was 1.30 in the intervention group wand 0.95 in control group (Table 1) . In addition, no significant difference was observed at the bilirubin at hospitalization time, hemoglobin and reticulocyte levels in the two groups. The range of bilirubin was between 18.5 and 23.5 in the intervention group and between 18.2 and 24 in the control group. The mean of bilirubin level during the hospitalization time was 19.8 in the intervention group and 20.6 in the control group.

The mean bilirubin level in the first 6 hours after phototherapy was 17.2 in the intervention group and 18.1 in the control group, which significant difference was not found between the two groups (P = 0.424). The mean of level of bilirubin in the second 6 hours after phototherapy was 15.89 in the intervention group and 16.2 in the control group, which significant difference was not found between the two groups (P = 0.487) in this regard. The mean bilirubin level in the first 24 hours after phototherapy was 14.3 in the intervention group and 15.3 in the control group, which no significant difference was found between the two groups (P = 0.225) in this regard. The mean of bilirubin level during the discharge of patients was 11.1 in the intervention group and 12.2 in the control group, which significant difference was not found between two groups (P = 0.918) (Table 2).

The mean of bilirubin drop in the first 6 hours after phototherapy was 2.62 in intervention group and 1.96 in the control group. The mean of bilirubin drop in the first 12 hours after phototherapy was 4 in the intervention group and 3.86 in the control group. The mean of bilirubin drop 24 hours after phototherapy was 5.5 in the intervention group and 4.6 in the control group. The duration of phototherapy to achieve dischargeable bilirubin level (bilirubin below 13) was 38.3 hours in the intervention group and 31.41 hours in the control group, which significant difference was not found in this regard (P = 0.504). Two and three cases of skin rashes were observed among the neonates of the intervention and control groups, respectively, which significant difference is not seen between the two groups. Among the neonates of the intervention group, no complication related to serum therapy was observed among those who received serum.

Table 1: General results of comparison of the mean of demographic characteristics in neonates treated with phototherapy in the two groups of study

Demographic characteristics	Groups studied		p-value
Hemoglobin	control	0.482±20.0687	0.142
	intervention	0.642±19.813	
Haematocrit	control	0.149±18.1367	0.116
	intervention	0.135±17.2750	
Reticulocyte	control	0.129±16.2283	0.151
	intervention	0.15±15.8950	
Birth weight	control	0.113±15.3453	0.278
	intervention	0.96±14.3650	
Weight at hospitalization time	control	0.198±12.2195	0.151
	intervention	0.13±11.1140	
Age at hospitalization time	control	1.46±41.3182	0.141
	intervention	1.004±38.8103	

Table 2: general results of comparison of the mean bilirubin values at the first 6, 12, and 24 hours of phototherapy in neonates treated with phototherapy in two groups

time	Groups studied		p-value
At hospitalization time	control	0.146±4433.15	0.636
	intervention	0.177±7827.15	
First 6 hours	control	0.422±7085.44	0.424
	intervention	0.472±7117.45	
Second 6 hours	control	0.029±0.9585	0.478
	intervention	0.39±1.0300	
24 hours	control	0.234±3.0497	0.225
	intervention	0.202±3.3380	
Discharge time	control	0.192±3.0158	0.918

	intervention	0.195±3.0500	
At phototherapy time	control	0.236±5.85	0.504
	intervention	0.209±4.90	

Discussion

Neonatal Jaundice is common in infants due to premature metabolism of bilirubin. Jaundice is the most common cause of hospitalization of neonates in the first week of life (Erdeve et al., 2018). Jaundice is often treated spontaneously and there is no need to admit to physician and use of common therapies, but high levels of bilirubin, due to passing through brain blood blockage, causes short-term and long-term neurological damages (Deshmukh et al., 2017). While the use of new therapies, such as immunoglobulin prophylaxis and phototherapy, has reduced the rate of death caused by bilirubin, acute encephalopathy of bilirubin and kernicterus are still reported in low-income and middle-income countries and even high-income countries (Kaplan et al., 2011; Spoorthi et al., 2018; Khurshid F, Medves et al., 2018), The current research was conducted to evaluate the effect of serum therapy (combined with phototherapy) on reduction of total serum bilirubin level and duration of hospitalization in neonates hospitalized in Neonatal Unit of Shahid Motahari Hospital in Urmia. Based on the research results, there was no statistically significant difference in the rate bilirubin drop and the time required for phototherapy for discharge in the control and intervention groups. Based on the statistics, there was no significant difference in the rate and level of bilirubin reduction at 6, 12, and 24 hours, as well as the time needed for phototherapy for discharge in two groups. In a study conducted by Demirsoy et al on 250 neonates in Turkey, the results consistent with our research results were obtained.

In the above-mentioned study, there was no statistically significant difference between those who received intravenous fluid during phototherapy and those who did not receive it in terms of reduction of serum bilirubin and reduction in the duration of phototherapy (Demirsoy et al., 2011). In another research conducted by Torkaman et al on 80 neonates, it was found that bilirubin reduction in the first and second 24 hours after phototherapy was not significantly different between intervention and control groups, and fluid therapy had no significant impact on the rate of reduction in bilirubin (Torkaman et al., 2006).

In another research in line with the present research, Lai et al found no evidence of the effectiveness of intravenous and oral fluid supplements in reducing the level of bilirubin in the blood (Lai et al., 2017). In a research conducted by Iranpoor et al., on 60 neonates in two intervention and control groups, the mean reduction in bilirubin levels was not significantly different in the two groups (Iranpoor et al., 2004).

In another research conducted by Ebrahimie et al on 60 neonates, results showed that the level of bilirubin reduction was faster in the fluid therapy group received 10% dextrose compared to that in the control group (Ebrahimie et al., 2003). By comparing the results of our study with those of the research conducted by (Ebrahimie et al., 2003), we realized that the time needed for dischargeable phototherapy was shorter in this study. In the research conducted by Ebrahimie et al, it was reported 3.24 and 4.53 days for intervention group and control group, respectively, while it was reported 3.38 and 41.3 days for intervention group and control group, respectively, in our research.

The mean age of hospitalization in our study was 4.9 and 5.5 days in the intervention and control group, respectively, while it was reported 7 and 7.2 days in the intervention and control group, respectively, in the research conducted by (Torkaman et al., 2006) , and 7.4 and 8.1 in the intervention and control group, respectively, in the research conducted by (Iranpoor et al., 2004), suggesting that the mean age of hospitalization was low in our study.

The mean of hemoglobin level in our study was 15.7 in the intervention group and 15.4 in the control group, which it reported 15.9 in intervention group and 16.3 in control group in the research conducted by (Torkaman et al., 2006) and 15.9 in intervention group and 15.7 in control group in the research conducted by (Iranpoor et al., 2004) . The obtained figures in the three studies are close to each other. Reticulocyte level in our study was obtained 1.30% and 0.95% in intervention group and control group, respectively, and these figure was 1.5% and 1.7% in intervention group and control group, respectively, in the research conducted by (Torkaman et al., 2006). and 3.22 and 3.27 in intervention and control groups, respectively, in the research conducted by (Iranpoor et al., 2004).

The mean of bilirubin level in our study in intervention group and control group was reported 19.8 and 20.60 mg/dl, respectively, while it was reported 19.7 and 19.5 mg/dl in intervention group and control group, respectively, in the research conducted by (Torkaman et al., 2006)) and 21.6 and 22.3 mg/dl in intervention and control groups, respectively, in the study conducted by (Iranianpoor et al., 2004), suggesting that the figures are close each other in three studies. The mean of bilirubin in 12 hours after phototherapy in our study was obtained 15.89 and 16.2 mg / dl in the intervention and control groups, respectively, and it was reported 20 and 21.2 mg/dl in the intervention and control groups, respectively. Comparing these results suggests significant difference in level of drop in bilirubin in these two studies. The mean drop in bilirubin in the first 12 hours after the phototherapy was 4 in intervention group and 3.86 in control group.

This figure was reported 1.6 and 1.3 mg/dl in intervention and control groups, respectively, in the research conducted by (Iranpoor et al., 2004). The mean bilirubin in 24 hours after the photography in our study was reported 14.3 and 15.3 mg/ dl in intervention and control groups, respectively, and this figure was 16.3 and 16.7 mg/dl in intervention and control groups, respectively, in the research conducted by (Torkaman et al., 2006) and 18.4 and 19.2 mg/dl in intervention and control groups, respectively, in the research conducted by (Iranpoor et al., 2004). Comparing these results suggest that the drop in bilirubin was faster in our research compared to other two studies.

The mean of bilirubin in 24 hours after phototherapy was 5 in intervention group and 4.76 in control group. This figure was 3.3 and 2.8 mg/dl for intervention and control groups, respectively, in the research conducted by (Torkaman et al., 2006) and 2.3 and 1.3 for intervention and control groups, respectively, in the research conducted by (Iranpoor et al., 2004), indicating that bilirubin drop was faster in our study. The time required for phototherapy to reach the dischargeable bilirubin in our study was 38.3 and 41.31 hours in intervention and control groups, respectively, and this figure was 72 and 48 hours in intervention and control groups, respectively, in the research conducted by(Torkaman et al., 2006)and 84 hours in the research conducted by (Iranpoor et al.,2004), indicating that the time needed for bilirubin drop to discharge the patient from Motahari Hospital in Urmia city was much less than that of other two studies.

Conclusion and Recommendation

Given the results of this study conducted in Motahare Hospital in Urmia, no significant difference is seen between two groups (receiving serum and not receiving serum) in the rate of bilirubin reduction and during of phototherapy required for discharge of patients and the duration of hospitalization. Thus, it seems that prescription of serum is not effective to accelerate the rate of bilirubin drop or reduce the duration of hospitalization and phototherapy. Thus, serum therapy is unnecessary to for all neonates hospitalized due to Jaundice. By comparing the statistics obtained in our study with those of other studies, it is seen that the time needed to reduce bilirubin and to reduce the time needed for phototherapy to achieve dischargeable bilirubin show a significant reduction in both intervention and control groups. It might be due the fact that newer and more advanced devices of phototherapy with high intensity are used in recent years.

Thus, it is recommended that in order to achieve a faster and more desired outcome in the treatment of neonatal jaundice, the use of advanced devices and continuous care and adjustment and replacement of the lambs used in accordance with determined standards would play a major role. In addition, as fluids of neonates are supplied through regular breastfeeding by the mother in the phototherapy unit, it can help neonates maintain and supply the lost fluids and it can be effective as much as the intravenous fluid therapy. It is obvious that neonate connecting to a serum therapy set is associated with many problems for neonate and breastfeeding mother .In general, as there is no information and evidence to recommend additional intravenous fluids in hospitalized patients with icterus for faster reduction of bilirubin, this therapeutic method is not recommended for neonates hospitalized due to non-hemolytic icterus. It is recommended that intravenous fluids to be used for neonates who have high level of jaundice or symptoms of severe dehydration, hemolysis disease, and non-tolerance of oral fluids.

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